Neuroblastoma and tooth abnormalities: a common history?

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Neuroblastoma, a malignant tumor of the sympathetic nervous system and the most common extracranial solid tumor in childhood, arises from embryonic neural crest cells. Tooth development begins before birth and continues for 12-14 years with the development of the third molar for several years. Abnormal events that occur during odontogenesis give permanent damage. Whereas the impact of multimodal therapy including radiotherapy and chemotherapy is major in tooth development defects [1] we suggested that the particular association between neuroblastoma and the occurence of missing teeth is not necessary due to treatment effects but considered the hypothesis of a common underlying genetic defect because of common cell origin.

Dental data were obtained via medical or dental records for 12 patients treated for neuroblastoma at the Pediatric Oncology and Hematology department in the University Hospital of Rennes (France). Panoramic radiographs could be effectively performed in seven patients. We observed dental disturbances in 8 patients including oligodontia for five (table 1). For 4 of them, we note the MYCN amplification in neuroblastoma cells. All but one were treated with one or more chemotherapeutic agents incriminated in tooth defect development and underwent a transplant. It would be attractive to incriminate the treatment effects as the cause of the dental abnormalities onset, because of the young age at NBL diagnosis contemporary to the most active dental development period. Furthermore, their treatment consists in multimodal therapy and used drugs commonly associated with dental defects in rodent experimentations [2, 3]. In our study, oligodontia was also present in children under 3 years but this finding is not surprising because of the neuroblastoma median age of 2. Also we note the occurrence of both crown and eruption dental abnormalities in one patient (patient 11) treated with chemotherapy and autologous stem cell transplantation but at age 10.

While prevalence of dental agenesis is around 5% in general population [4], a recent study found a prevalence of 16.2% missing teeth in childhood cancer survivors treated from 0 to 7 [5]. Even if chemotherapy and total bone irradiation radiotherapy are likely to be etiological factors, it cannot be ruled out that regarding neuroblastoma, a developmental etiology could be considered. So intringuing, four of five patients with tooth agenesis presented a MYCN gene amplification. The proto-oncogene *MYCN* is mainly expressed during neural development [6] and frequently amplified in advanced-stage neuroblastoma associated with poor prognosis. *MYCN* might stimulate neuroblastoma cell proliferation by inhibiting negative regulators of the Wnt signaling [7]. Furthermore, while germline mutations in the transcription factor *PHOX2B* gene have been reported in sporadic and familiar forms of neuroblastoma [8, 9], the *MSX1* target is known to be associated with tooth agenesis [10, 11]. Interestingly, *MSX1*, an important homeobox gene in embryonic neural crest development, was shown to be down regulated after inducible expression of *PHOX2B* [12]. This PHOX2B target is involved in both embryonic developmental pathways Delta-Notch and Wnt [12, 13]. Whereas links between cancer predisposition and dental abnormalities are well known for adulthood cancers involving disruption of the Wnt signalling (germline *AXIN2* mutations, Gardner syndrome), we could emphasize that a dysregulation of the Wnt signaling pathway could take part in alteration of dental genesis and neuroblastoma tumorigenesis.

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